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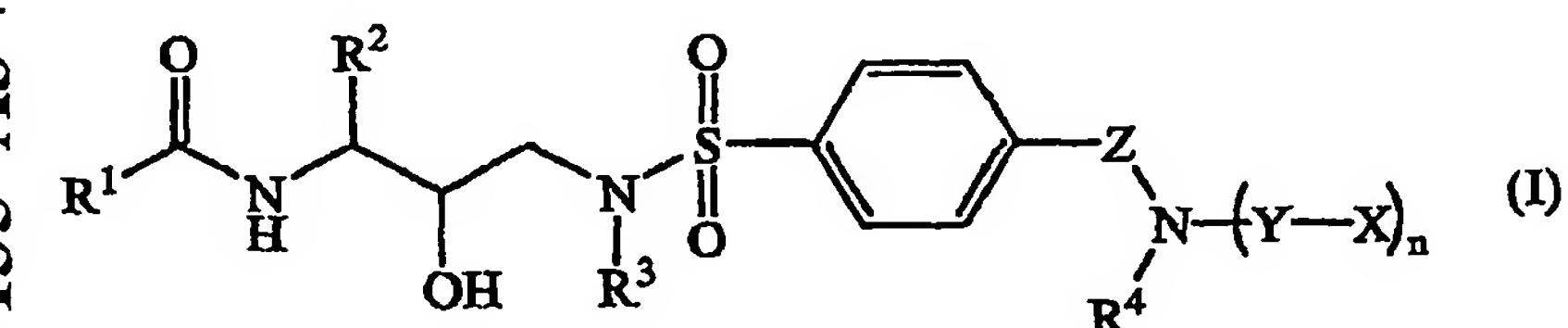
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

(54) Title: HIV PRODRUGS CLEAVABLE BY CD26

(57) Abstract: The present invention provides new prodrugs which are conjugates of a therapeutic compound and a peptide wherein the conjugate is cleavable by dipeptidyl-peptidases, more preferably by CD26, also known as DPPIV (dipeptidyl aminodipeptidase IV).



(I), the stereoisomeric forms and salts thereof, wherein n is 1 to 5; Y is proline, alanine, hydroxyproline, dihydroxyproline, thiazolidinecarboxylic acid (thioproline), dehydroproline, pipecolic acid (L-homoproline), azetidinecarboxylic acid, aziridinecarboxylic acid, glycine, serine, valine, leucine, isoleucine and threonine; X is selected from any amino acid in the D- or L-configuration; X and Y in each repeat of [Y-X] are chosen independently from one another and independently from other repeats; Z is a direct bond or a bivalent straight or branched saturated hydrocarbon group having from 1 to 4 carbon atoms; R<sup>1</sup> is an aryl, heteroaryl, aryloxy, heteroaryloxy, aryloxyC<sub>1-4</sub>alkyl, heterocycloalkyloxy, heterocycloalkylC<sub>1-4</sub>alkoxy, heteroaryloxyC<sub>1-4</sub>alkyl, heteroarylC<sub>1-4</sub>alkyloxy; R<sup>2</sup> is arylC<sub>1-4</sub>alkyl; R<sup>3</sup> is C<sub>1-10</sub>alkyl, C<sub>2-6</sub>alkenyl or C<sub>3-7</sub>cycloalkylC<sub>1-4</sub>alkyl; R<sup>4</sup> is hydrogen or C<sub>1-4</sub>alkyl. The present invention furthermore provides the use of said prodrugs as medicines as well as a method of producing said prodrugs.



- *with sequence listing part of description published separately in electronic form and available upon request from the International Bureau*

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**A. CLASSIFICATION OF SUBJECT MATTER**  
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According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97/45117 A (PROTOTEK INC ; SMITH ROBERT E (US)) 4 December 1997 (1997-12-04) the whole document -----	1-31
A	WO 00/71571 A (BOEHRINGER SOHN INGELHEIM ; GARIN CHESA PILAR (DE); RETTIG WOLFGANG J) 30 November 2000 (2000-11-30) the whole document ----- -/-	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

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## INTERNATIONAL SEARCH REPORT

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## C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BALAJTHY Z ET AL: "SYNTHESIS AND FUNCTIONAL EVALUATION OF A PEPTIDE DERIVATIVE OF 1-BETA-D-ARABINOFURANOSYLCYTOSINE" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 35, no. 18, 1992, pages 3344-3349, XP002939110 ISSN: 0022-2623 the whole document -----	
A	TROUET A ET AL: "Extracellular tumor - activated prodrugs for the selective chemotherapy of cancer: application to doxorubicin and preliminary in vitro and in vivo studies" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 61, no. 7, 1 April 2001 (2001-04-01), pages 2843-2846, XP002204750 ISSN: 0008-5472 the whole document -----	
A	US 5 962 216 A (BAURAIN ROGER ET AL) 5 October 1999 (1999-10-05) the whole document -----	
A	MASQUELIER M ET AL: "AMINO ACID AND DIPEPTIDE DERIVATIVES OF DAUNORUBICIN. 1. SYNTHESIS, PHYSICOCHEMICAL PROPERTIES, AND LYSOSOMAL DIGESTION" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 23, no. 11, 1980, pages 1166-1170, XP000914522 ISSN: 0022-2623 the whole document -----	
A	WO 99/67278 A (MANHART SUSANNE ; DEMUTH HANS ULRICH (DE); HOFFMANN TORSTEN (DE); PROB) 29 December 1999 (1999-12-29) the whole document -----	
A	ANAND BANMEET ET AL: "Novel dipeptide prodrugs of acyclovir for ocular herpes infections: Bioreversion, antiviral activity and transport across rabbit cornea." CURRENT EYE RESEARCH. 2003 MAR-APR, vol. 26, no. 3-4, March 2003 (2003-03), pages 151-163, XP009036464 ISSN: 0271-3683 the whole document -----	

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/050753

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>AUGUSTYN S K ET AL: "THE UNIQUE PROPERTIES OF DIPEPTIDYL-PEPTIDASE IV (DPP IV/CD26) AND THE THERAPEUTIC POTENTIAL OF DPP IV INHIBITORS". CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 6, no. 4, 1999, pages 311-327, XP000870290 ISSN: 0929-8673 the whole document</p> <p>-----</p> <p>YARON A ET AL: "PROLINE-DEPENDENT STRUCTURAL AND BIOLOGICAL PROPERTIES OF PEPTIDES AND PROTEINS" CRITICAL REVIEWS IN BIOCHEMISTRY AND MOLECULAR BIOLOGY, CRC PRESS, BOCA RATON, FL, US, vol. 28, no. 1, 1993, pages 31-81, XP000925565 ISSN: 1040-9238 the whole document</p> <p>-----</p> <p>DE MEESTER I ET AL: "CD26, let it cut or cut it down" IMMUNOLOGY TODAY, ELSEVIER PUBLICATIONS, CAMBRIDGE, GB, vol. 20, no. 8, 1 August 1999 (1999-08-01), pages 367-375, XP004177365 ISSN: 0167-5699 cited in the application the whole document</p> <p>-----</p> <p>WO 03/048190 A (MITRA ASHIM K ; UNIV MISSOURI (US)) 12 June 2003 (2003-06-12)</p> <p>the whole document</p> <p>-----</p> <p>WO 99/67254 A (UNIV ILLINOIS ; US HEALTH (US); ERICKSON JOHN W (US); GHOSH ARUN K (US) 29 December 1999 (1999-12-29) figure 5a</p> <p>-----</p> <p>BOONACKER EMIL ET AL: "The multifunctional or moonlighting protein CD26/DPPIV." EUROPEAN JOURNAL OF CELL BIOLOGY, vol. 82, no. 2, February 2003 (2003-02), pages 53-73, XP002302224 ISSN: 0171-9335 the whole document</p> <p>-----</p>	
P,X		1,11-13, 25,26, 31,32, 43,44, 50,51, 54,55
Y		1-31
Y		1-31

## INTERNATIONAL SEARCH REPORT

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PCT/EP2004/050753

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	OHTSUKI TAKASHI ET AL: "Good or evil: CD26 and HIV infection" JOURNAL OF DERMATOLOGICAL SCIENCE, vol. 22, no. 3, April 2000 (2000-04), pages 152-160, XP002302250 ISSN: 0923-1811 the whole document -----	1-31

**INTERNATIONAL SEARCH REPORT**
**Information on patent family members**
**International Application No**
**PCT/EP2004/050753**

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9745117	A	04-12-1997	AU CA CZ EP WO	3224997 A 2256669 A1 9803893 A3 0914123 A1 9745117 A1	05-01-1998 04-12-1997 14-07-1999 12-05-1999 04-12-1997
WO 0071571	A	30-11-2000	AU BG BR CA CN CZ EE WO EP HU JP NO NZ PL SK US ZA	6559100 A 106096 A 0010564 A 2369933 A1 1374969 T 20014097 A3 200100600 A 0071571 A2 1180116 A2 0202367 A2 2003500417 T 20015536 A 516075 A 351680 A1 16452001 A3 6613879 B1 200109151 A	12-12-2000 31-05-2002 19-02-2002 30-11-2000 16-10-2002 13-02-2002 17-02-2003 30-11-2000 20-02-2002 28-11-2002 07-01-2003 10-01-2002 26-03-2004 02-06-2003 05-03-2002 02-09-2003 17-12-2002
US 5962216	A	05-10-1999	BE BE AU AU WO CA EP JP NO NZ US US	1008580 A3 1008581 A3 694546 B2 3248695 A 9605863 A1 2203622 A1 0769967 A1 10508291 T 970748 A 291368 A 2002160943 A1 6342480 B1	04-06-1996 04-06-1996 23-07-1998 14-03-1996 29-02-1996 29-02-1996 02-05-1997 18-08-1998 10-04-1997 29-04-1999 31-10-2002 29-01-2002
WO 9967278	A	29-12-1999	DE AU AU BR CA CN WO EP HU JP NO NZ PL RU US US	19828113 A1 766726 B2 4900799 A 9911468 A 2335992 A1 1306540 T 9967278 A1 1087991 A1 0102281 A2 2003524591 T 20006484 A 508722 A 345151 A1 2226533 C2 2004171555 A1 2002049164 A1	05-01-2000 23-10-2003 10-01-2000 20-03-2001 29-12-1999 01-08-2001 29-12-1999 04-04-2001 28-11-2001 19-08-2003 19-12-2000 25-07-2003 03-12-2001 10-04-2004 02-09-2004 25-04-2002
WO 03048190	A	12-06-2003	WO	03048190 A2	12-06-2003
WO 9967254	A	29-12-1999	AU AU	771780 B2 4828099 A	01-04-2004 10-01-2000

**INTERNATIONAL SEARCH REPORT**

## Information on patent family members

International Application No

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9967254	A	AU	4828199 A	10-01-2000
		CA	2336160 A1	29-12-1999
		EP	1088098 A2	04-04-2001
		JP	2002518063 T	25-06-2002
		WO	9967417 A2	29-12-1999
		WO	9967254 A2	29-12-1999